Short-Call Abstracts

EXPOSURE TO HIGH THYROID HORMONE IN UTERO CAUSES PERMANENT REDUCED SENSITIVITY TO THYROID HORMONE

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Objectives: High maternal thyroid hormone levels have a deleterious effect on fetal growth and development. We have shown that unaffected fetuses carried by mothers with resistance to thyroid hormone due to mutations in the THRB gene (RTH-beta) are more often aborted, and when born, have lower weight and suppressed TSH. We also showed that serum TSH in adult unaffected mice born to dams with RTH-beta is less suppressible by T3.

Methods: Normal adult individuals (without THRB gene mutations), aged 22–54 yrs born to affected mothers and to affected fathers (n = 4: 3F and 1M in each group) and belonging to the same extended family with THRB R243Q mutation were given 200 μg L-T3 twice daily. Serum was collected at –15, 0, 15, 30, 45, 60, 90, 120 and 180 min after TRH. Analysis was done by ANOVA. Results are expressed as mean ± SD.

Results: Basal values of serum TSH, FT4, FT3, rT3, TG, and PRL were not significantly different, and after L-T3 treatment, both groups had equally expressed as mean ± SD.

Conclusions: Exposure to high thyroid hormone in utero reverts the sensitivity of the thyrotrophs to L-T3, producing persistent, subclinical RTH into adulthood.

TRIAC TREATMENT OF AN INFANT WITH ALLAN-HERNDON-DUDLEY SYNDROME (AHDS): EFFECTS ON IODOTHYRONINES IN SERUM AND CEREBRO-SPINAL FLUID

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Allan-Herndon-Dudley Syndrome (AHDS) is a devastating disease caused by defects in the thyroid hormone (TH) transporter MCT8. Systemic hyperthyroidism is heralded by elevated serum T3 (with mildly increased TSH and decreased T4). However, the brain is hypothyroid, causing incapacitating psychomotor retardation. Therapeutic attempts with PTU+Levothyroxine or the T3-analogue DITPA could normalize TH derangements without neurological improvement. Recently, administration of TETRAC to McRT KO mice corrected TH abnormalities in this model for AHDS.

Objective: To determine the TH metabolic and developmental effects of TRIAC (a rapidly-generated metabolite of TETRAC) in a child with early-diagnosed AHDS.

Patient and Methods: 8-month-old male with severe axial hypotonia, psychomotor retardation and apparent hypothyroidism (TSH 7.7 mU/L, FT4 0.48 ng/dL) but elevated FT3 (8.86 pg/mL). Thyroid-targeted CGH array (Thyroarray©). Compassionate treatment with increasing doses of TRIAC (10–40 μg/kg/day) for 1 year. Follow-up: TH profiles, brain MR and psychometry (Brunet-Lezine) every 3 months. Radioimmunoassay of T4, T3 and TRIAC in cerebrospinal fluid (CSF) of patient and 14 age-matched controls.

Results: Novel de novo MCT8 deletion spanning 25.04 Kb from mid-exon 3. TRIAC normalized FT3 and TSH (4.1 ng/mL) but reduced FT4 (0.3 ng/dL). Brain myelination progressed 5 months after 9-months treatment. After initial improvement of milestone acquisition, developmental deceleration occurred. Iodothyronines in CSF are low irrespective of treatment, suggesting blood-CSF barrier transport of T3-T4 is restricted in AHDS.
WHOLE GENOME SEQUENCE BASED ANALYSIS OF THYROID FUNCTION


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N = 2,287) and used an additional collection with WGS data (SardiNIA) and deeply imputed datasets (imputed to a joint 1000 genomes and UK10K reference panel) to perform a meta-analysis for common variants (MAF >1%) associated with TSH and FT4 (N = 16,335). We undertook analysis of exonic rare variants (MAF <1%) using sequence kernel association testing (SKAT) in 40 candidate genes and performed genome-wide complex trait analyses (GCTA) to explore the extent that common SNPs (MAF >1%) explained the variance in TSH and FT4.

Results: For TSH we report a novel variant at 3p25 (MAF = 23.5%, P = 6.15 × 10−6) and a new independent variant in PDE8B (MAF = 10.4%, P = 5.94 × 10−6). Expression quantitative trait locus analysis revealed our variant at 3p25 modulates gene transcription in adipose, skin and whole blood cells. Methylation profiles revealed evidence for methylation quantitative trait locus effects for our novel variant in PDE8B (P = 4.38 × 10−6). For FT4 we identified a low frequency variant in 18q11 (MAF = 3.2%, P = 1.27 × 10−7) tagging a rare functional variant in TTR (MAF = 0.4%, P = 2.14 × 10−5). SKAT analysis revealed a novel association with FT4 in chromosome 8p12 (P = 2.53 × 10−6). GCTA analysis estimated common SNPs (MAF >1%) explained 24% (95% CI 19, 29) and 20% (95% CI 14, 26) of TSH and FT4 variance, respectively (P ≤ 0.0001).

Conclusion: Our results demonstrate that increased coverage in WGS population association studies allows detection of both common and rare variants in thyroid function. Common variants collectively account for over 20% of the variance in TSH and FT4; a substantial advance on estimates from earlier genome-wide association studies.

EFFECTS OF EARLY LT4 TREATMENT IN A PATIENT WITH A MUTATION IN TRα1/α2

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Background: Patients with resistance to thyroid hormone due to inactivating mutations in TRα1 (RTHa) are characterized by growth retardation, delayed bone and motor development, cognitive defects, and abnormal TFTs. Recently, the first patients with a mutation in both TRα1 and its non-T3-binding splicing variant TRα2 have been identified. Here, we describe a young girl (15 mo) with a mutation in both TRα1 and TRα2.

Objective: To study the effects of early LT4 treatment.

Method: The patient was assessed before and during 6 mo of LT4 treatment at the age of 18 mo. In addition, we studied transcriptional activity of mutant (MT) vs. wild-type (WT) TRα1 in cells co-transfected with a TR-dependent promoter-reporter construct.

Results: At 15 mo, the patient presented with axial hypotonia, delayed motor development (Alberta Infant Motor Scale (AIMS) <55) and severe growth retardation (height –2.6 SDS). She also showed low serum (F)T4 and (F)T3, increased T3 and normal TSH levels. The patient has a D211G mutation in both TRα1 and TRα2, resulting in decreased transcriptional activity of TRα1, overcame at higher T3 levels (MT vs. WT TRα1 activity was 46% at 1 nM T3, and 78% at 100 nM T3). MT TRα1 showed little if any dominant activity towards WT TRα1. In addition, WT or MT TRα2 did not show a significant dominant-negative inhibition of WT or MT TRα1.

Six mo of LT4 treatment (3.5–4.7 μg/kg) resulted in a marked improvement of the hypothyronia, motor development (AIMS normalized) and growth (height increase of 0.76 SDS). She also showed low serum (F)T4 and (F)T3, increased T3 and normal TSH levels. The patient has a D211G mutation in both TRα1 and TRα2, resulting in decreased transcriptional activity of TRα1, overcame at higher T3 levels (MT vs. WT TRα1 activity was 46% at 1 nM T3, and 78% at 100 nM T3). MT TRα1 showed little if any dominant activity towards WT TRα1. In addition, WT or MT TRα2 did not show a significant dominant-negative inhibition of WT or MT TRα1.

Conclusion: This case emphasizes the importance of identifying patients with TRα mutations at a very young age, since early LT4 treatment may lead to clear clinical improvement.